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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,360	12/21/2006	Paul J. Hergenrother	ILL01-009-US	8169

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EXAMINER	
BLAND, LAYLA D	
ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,360	HERGENROTHER ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,20-39,54 and 55* is/are pending in the application.

4a) Of the above claim(s) *25-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18, 20-24, and 54-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is a response to Applicant's amendment submitted February 25, 2009, wherein claim 18 is amended, claim 19 is canceled, and claims 54 and 55 are newly submitted.

Claims 18, 20-39, and 54-55 are pending. Claims 25-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 4, 2008.

Claims 18, 20-24, and 54-55 are examined on the merits herein.

Withdrawn Rejections/Objections

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18, 20-23, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al. (Analytical Biochemistry 68, 54-61 (1975), PTO-1449 submitted August 8, 2007) in view of Osawa et al. (Journal of Clinical Microbiology, Apr 1997, p. 951-953, of record), as evidenced by Nakamura et al. (Analytical Chemistry, vol. 50, No. 14, December 1978, PTO-1449 submitted August 8, 2007).

Clark et al. teach that NAD+ and similar molecules can be detected after being converted to a fluorescent compound by treatment with acetophenone in KOH followed by formic acid [page 61, Discussion]. Using that method, N^1-methylnicotinamide levels in human sera were measured [page 60, first full paragraph]. Only N^1-alkylpyridinium derivatives of nicotimamide give fluorescent products under the conditions of the assay [page 61, second paragraph].

Clark et al. do not teach detection of NAD+ in the presence of an enzyme.

Osawa et al. teach a method which uses NAD degradation as a biochemical marker for identifying CT-producing *V. cholerae* O1 and O139. CT subunit A has NADase activity. [page 951, first two paragraphs]. After incubation of seven strains of *V. cholerae* with NAD solution in PBS, the concentration of NAD remaining in each well was measured by color [page 951, Development of an assay system]. Wells containing NAD at more than 80 umol/liter gave a distinct red color, while the ones containing NAD at a concentration of less than 30 umol/liter gave only a faint pink color [page 952, first full paragraph]. Thus, NADase activity was measured by detecting incubating NAD with the enzyme and measuring remaining NAD.

Nakamura teaches that acetophenone has been used for fluorimetric determination of NAD+. The procedure involves reaction of NAD+ and acetophenone in alkaline media and successive heating with excess acid which produces fluorophores [page 2047, second paragraph]. A proposed mechanism of the reaction is shown in Scheme 1 [page 2047]. Another possibility for the structure of the fluorophore is the γ-adduct at C4 [page 2050, second column, end]. The γ-adduct, cyclized at C4, is the compound shown in instant claim 18.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Clark et al. for measuring activity of a NAD+ utilizing enzyme. Clark teaches measurement of N^1-methylnicotinamide by conversion to the fluorescent compound, and teaches that NAD+ may also be converted to a fluorescent compound in the same way. Measuring the activity of an NAD+ utilizing enzyme via measurement of NAD+ is known in the art, as taught by Osawa, and the skilled artisan could reasonably expect Clark's method of measuring NAD+ to be useful for the same purpose. Nakamura is cited to establish that the method of Clark et al. produces compound 1 of the instant claims.

Response to Arguments

Applicant argues that Clark's fluorescent compound was not the compound shown in instant claim 18 because Clark didn't characterize the product and didn't heat the reaction when formic acid was added, and because the mechanism shown by Nakamura doesn't result in the compound of claim 18. The argument that Clark didn't characterize the product is not persuasive, because Clark prepared the compound in

the same way as recited in instant claim 20, and in the same was as taught by Nakamura, so it is expected that the same product formed. The argument that heating is required to form the fluorophore is not persuasive because Nakamura teaches that "the formation of acetophenone fluorophore in formic acid was slow at 0ºC," and "allowing the reaction mixture of the first step to stand at 0ºC for 30 min in the formic acid solution did not cause any side-reaction except the gradual transformation to the fluorophore." Thus, the fluorophore is formed slowly, in some amount, in 30 min at 0ºC. It is noted that Clark's procedure is 4-6 hours at room temperature [page 56, third paragraph]. Since the fluorophore forms slowly at 0ºC, it is expected that it also forms at room temperature, likely at a faster rate than at 0ºC. Further, because Nakamura teaches that the fluorophore forms faster at 50ºC and even faster at 95ºC [page 2049, Conversion of the Intermediate to Fluorophore], the skilled artisan would have been motivated to employ a heating step in order to speed the reaction. Applicant's argument regarding Nakamura's proposed mechanism is not persuasive because Nakamura also teaches that the γ-adduct can be formed.

Applicant argues that no fluorescence-based methods are used or suggested by Osawa. This argument is not persuasive because fluorescence-based methods of detecting NAD+ are used by Clark. The teachings of Clark in *combination* with Osawa lead the skilled artisan to claimed invention, as discussed above.

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clark in view of Osawa, as evidence by Nakamura, as applied to claims 18-23 above, and

further in view of Pieper et al. (PNAS, February 15, 2000, vol. 97, no. 4, 1845-1850, of record).

Clark and Osawa teach as set forth above, fluorometric measurement of NAD+ which the skilled artisan could use for measuring the activity of an NAD+ utilizing enzyme.

Clark and Osawa do not teach measurement of the activity of PARP.

Pieper et al. teach that Poly(ADP-ribose) polymerase-1 (PARP-1) catalyzes polymerization of ADP-ribose from its substrate NAD+. Through PARP activation, NAD+ is substantially reduced. [page 1845, first paragraph]. Basal *in vivo* neuronal PARP activity is diminished and basal NAD+ levels are elevated after treatment with NMDA-R antagonists, free radical scavengers, and nNOS inhibitors [page 1845, third paragraph].

It would have been obvious to one skilled in the art at the time the invention was made to carry out the method as described above, for measuring the activity of PARP. PARP utilizes NAD+, as does CT subunit A (as taught by Osawa), and the correlation between NAD+ concentration and PARP activity is established by Pieper. Thus, the skilled artisan could conceive of using Clark's method of measuring NAD+ for measuring the activity of PARP.

The following new rejection was necessitated by Applicant's amendment submitted February 25, 2009, wherein new claim 54, requiring the measurement of aldehyde dehydrogenase, was added.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 54 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clark in view of Osawa, as evidence by Nakamura, as applied to claims 18-23 above, and further in view of Hilton (Cancer Research 44, 5156-5160, November 1984).

Clark and Osawa teach as set forth above, fluorometric measurement of NAD+ which the skilled artisan could use for measuring the activity of an NAD+ utilizing enzyme.

Clark and Osawa do not teach measurement of the activity of aldehyde dehydrogenase.

Hilton teaches a method wherein aldehyde dehydrogenase was determined by measurement of NAD consumption [page 5157, second paragraph].

It would have been obvious to one skilled in the art at the time the invention was made to carry out the method as described above, for measuring the activity of aldehyde dehydrogenase. Aldehyde dehydrogenase utilizes NAD, and the activity of an aldehyde dehydrogenase has been determined by consumption of NAD, as taught by Hilton et al. The skilled artisan knows that activity of NAD-utilizing enzymes can be determined by measurement of remaining NAD, as taught by Osawa. Clark teaches a

method for measuring NAD fluorimetrically. Thus, the skilled artisan would have a reasonable expectation that the activity of NAD-utilizing enzymes could be determined by conversion of remaining NAD to the fluorophore, as taught by Clark et al., followed by measurement of that compound.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/Layla Bland/
Examiner, Art Unit 1623